REMARKS

The specification has been amended to add the well-known generic description of the trademark product "SEPHAROSE" at the appropriate place in Applicants' specification. Support for this amendment is found throughout Applicants' specification, e.g., in the use of the trademark term, in view of the knowledge of those of ordinary skill in the art. No new matter is added.

Claims 1- 24 are pending. Non-elected claims 25-53 have been cancelled. The preamble of claim 1 has been amended for the sake of clarity to recite a method for "preparing a plasmin solution." This amendment is supported throughout Applicants' specification. Also, claim 1 has been amended to recite that the resulting plasmin solution has "a pH of approximately 1 to 4." Support for this amendment can be found throughout Applicants' specification, e.g., at page 8, line 31. Claim 15 has been amended to replace tPA with "tissue plasminogen activator." Claim 17 has been amended to replace the trademark "SEPHAROSE" with "a beaded form of agarose gel." This amendment is supported as noted above regarding the amendment of the specification. Claim 19 has been amended to delete the phrase "derivatives thereof" and to correct the typographical error whereby the term "alanine" was repeated in the group list.

No new matter has been added.

Objection to the Specification

The Examiner objected to the specification, asserting that any use of the trademark term "SEPHAROSE" should be capitalized wherever it appears and should be accompanied by the generic terminology. Office Action at page 2.

Applicants note that all occurrences of SEPHAROSE in the specification are rendered in all capital letters. In the foregoing amendment, Applicants have introduced the phrase "a beaded form of agarose gel" in a paragraph of the original text to provide further generic explanation of the term SEPHAROSE. Applicants submit that this phrase provides an explicit description of what would be understood by one of ordinary skill in the art from the previous use of the trademark SEPHAROSE without direct recitation of such language.

Based on the addition of the further explanation of the term and the consistent use of full capitalization, Applicants respectfully submit that any asserted basis for the objection is now moot. Accordingly, Applicants respectfully request that the objection be withdrawn.

Rejections under 35 U.S.C. § 112 are Rendered Moot

The Examiner rejected claims 1-24 as allegedly indefinite. Based on the foregoing amendment and the following remarks, Applicants respectfully traverse the rejection.
The Examiner asserted that claim 1 was indefinite due to the recitation of a buffering step in claim 1 when the preamble recites "[a] method of purifying plasmin." Office Action at page 3. Although Applicants believe that previous claim language was not indefinite in any respect (i.e., a buffering step is not *inconsistent* with a method of purifying plasmin), Applicants have amended the preamble of claim 1 (from which claims 1-24 depend, either directly or indirectly) to recite a method of "preparing a plasmin solution." Accordingly, any asserted basis for the rejection is now rendered moot. The scope of the claims is unaffected and no new issues are raised, and Applicants respectfully request that the rejection be withdrawn.

The Examiner asserted that claims 1, 18, and 19 are indefinite based on their recitation of the phrase "low pH." Office Action at page 3. Although it is Applicants' position that the phrase "low pH" was defined sufficiently in Applicants' original claims and specification such that it would be readily understood by one of ordinary skill in the art, Applicants have amended claim 1 to add a recitation that the resulting plasmin solution has "a pH of approximately 1 to 4." It is believed that this amendment provides additional clarification regarding the recitations of "low pH" mentioned by the Examiner and that any asserted basis for the rejection is now moot. Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

The Examiner alleged that claims 8-10 and 14 were indefinite because they "are not set forth in terms of a positive statement." Office Action at page 4. Applicants' claim 1 (from which claims 8-10 and 14 depend directly or indirectly) originally recited "[a] method for purifying plasmin" and now recites "[a] method for preparing a plasmin solution." Applicants note that both original and amended claim 1 recite a step of "cleaving a plasminogen in the presence of a plasminogen activator to yield an active plasmin." It seems abundantly clear that the phrases objected to by the Examiner in claims 8-10 and 14 refer to this step and modify this element of the claimed process appropriately. Although Applicants are not entirely sure what

was intended by the Examiner's statement as quoted above, it is believed that any possible confusion based on the particular language of the original preamble of claim 1 is now moot. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

The Examiner alleged that claim 15 was indefinite for use of the abbreviation "tPA" for the term "tissue plasminogen activator." Applicants have amended the claim as suggested by the Examiner. Accordingly, any asserted basis for the rejection is now moot, and the rejection must be withdrawn.

The Examiner alleged that claim 17 was infinite for the recitation of the trademark "SEPHAROSE." Applicants have amended the claim to recite "cross-linked agarose" as a generic description of the product SEPHAROSE. Accordingly, any asserted basis for the rejection is now moot, and the rejection must be withdrawn.

The Examiner alleged that claim 19 was infinite for the recitation of the phrase "derivatives thereof." Applicants have amended the claim to delete this language. Further, the informality where the group member "alanine" was repeated has been corrected by deletion of the latter occurrence. Accordingly, any asserted basis for the rejection is now moot, and the rejection must be withdrawn.

Rejections under 35 U.S.C. § 102 are Traversed

The Examiner rejected claims 1-3, 8-15, and 18-23 as allegedly anticipated by Robbins, K.C., *et al.*, *J. Biol. Chem.*, *238*:952-962 (1963) (Robbins). Based on the following remarks, Applicants respectfully traverse the rejection.

Applicants' sole independent claim, claim 1 recites the following step:

> substantially removing the plasminogen activator from the active plasmin by binding the active plasmin to an *active plasmin-specific absorbent material* to form a bound plasmin, and eluting the bound plasmin with an excipient solution having a pH from about 2.5 to about 9.0 to form a plasmin solution . . . .

Emphasis added. In the third paragraph of the Summary section of Applicants' specification, i.e., at page 5, lines 7-12, Applicants provide the following explanation of what an "active plasmin-specific absorbent material" is:

> The plasminogen activator can be removed from the active plasmin by binding the active plasmin to an active plasmin-specific absorbent material to form a bound plasmin. One such active plasmin-specific absorbent material can comprise benzamidine. Once bound, the active plasmin can be eluted with a low

pH solution to form a final plasmin solution. Plasminogen activator may also be further removed by hydrophobic interaction.

From reading Applicants' specification, one of ordinary skill in the art would readily understand that an "active plasmin-specific absorbent material" as recited in Applicants' claims means an absorbent material that is specific for "active plasmin."

The Examiner cited sections of the Robbins reference relating to alleged further purification of plasmin by gel filtration or DEAE (see pages 956 and 957 of Robbins). However, nowhere does Robbins disclose the step recited in Applicants' claim of "substantially removing the plasminogen activator from the active plasmin by binding the active plasmin to an *active plasmin-specific absorbent material* to form a bound plasmin, and eluting the bound plasmin . . . ."

The Examiner has not asserted that Robbins discloses the use of any absorbent material that is specific for active plasmin as recited in Applicants' claims and taught in their specification. For at least this reason, Robbins could not possibly have anticipated Applicants' claimed invention.

Rejections under 35 U.S.C. § 103 are Traversed

Robbins in view of Sherry, Castellino, Morii, and Wiman

The Examiner rejected claims 1-4, and 8-23 as allegedly unpatentable over Robbins in view of Sherry, *J. Amer. Coll. Cardiol.* (1989) (Sherry); Castellino, *Meth. Enzymology 80*:365-378 (1981) (Castellino); Morii, EP 0256836 A1 (Morii), and Wiman, *Biochem. J. 191(1)*:229-232 (1980) (Wiman). Based on the foregoing and following remarks, Applicants respectfully traverse the rejection.

Applicants have noted that Robbins fails to disclose any step involving an "active plasmin-specific absorbent material" as presently claimed. Further, Robbins fails to teach or suggest any such step or material. The Examiner does not assert that any of the secondary references cure this deficiency of Robbins. In fact, it does not appear that any of the cited secondary references teach or suggest any such material or step.

For at least the reason that neither Robbins nor any of the cited secondary references teach or suggest any step involving an "active plasmin-specific absorbent material," no

combination of any teaching thereof could have provided Applicants' claimed invention. Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Robbins, Sherry, Castellino, Morii, and Wiman

In view of Silver, Yago, and Diedrichsen

The Examiner rejected claims 1-5, and 8-24 as allegedly unpatentable over Robbins, Sherry, Castellino, Morii, and Wiman, in view of US Pat. No. 6,479,253 to Silver, et al. (Silver), US Pat. No. 5,879,923 to Yago, et al. (Yago), and US Pat. No. 4,462,980 to Diedrichsen, et al. (Diedrichsen). Based on the foregoing and following remarks, Applicants respectfully traverse the rejection.

As noted above Robbins, Sherry, Castellino, Morii, and Wiman fail to teach or suggest any step involving an "active plasmin-specific absorbent material." Silver, Yago, and Diedrichsen also fail to teach or suggest such a step or material.

Although the Examiner notes a section of Silver (Col. 30, lines 29-42) describing removal of serine proteases generally from a "prepupal larval protein pool enriched for carboxylesterase activity" using "p-aminobenzamidine cross-linked to Sepharose beads," this is not the claimed step of Applicants' invention calling for "substantially removing the plasminogen activator from the active plasmin by binding the active plasmin to an active plasmin-specific absorbent material to form a bound plasmin, and eluting the bound plasmin . . . ." In the second passage of Silver cited by the Examiner (col. 22, lines 36-42), the Examiner notes correctly that Silver mentions affinity chromatography generally, in a description of what is meant by the phrase "purification of proteins." This passage is completely general, and refers to no particular protein. However, if one were to assume that this very general passage referred to proteins that are the subject of Silver, then it would be taken to refer to "serine protease *inhibitor* proteins" (emphasis added) and not serine proteases. See Silver throughout, e.g., in the Abstract and Title. Based on the Examiner's comments at page 22 of the Office Action, she appears to have believed that Silver related to the purification of serine proteases. However, Silver relates to serine protease *inhibitors*.

Silver does not mention plasmin. Further, Silver only describes a method of *removing* serine proteases generally from a complex mixture, where the unbound fraction is the desired product (proteins having carboxylesterase activity), i.e., in the first cited passage of Silver

discussed above. No one of ordinary skill in the art would understand this aspect of Silver to teach the use of "an active plasmin-specific absorbent material" to bind and retain active plasmin for the purpose set forth in Applicants' claimed method. No description of the removal of serine proteases as contaminants from a crude protein preparation would suggest the Applicants' claimed method which includes removing plasminogen activator from active plasmin using an "active plasmin-specific absorbent material."

No reference teaches or suggests "substantially removing the plasminogen activator from the active plasmin by binding the active plasmin to an active plasmin-specific absorbent material to form a bound plasmin, and eluting the bound plasmin . . . ." Accordingly, no combination of any teaching thereof could have provided Applicants' claimed invention. Further, even if one considered any teaching of Silver to be relevant, there would have been no motivation to combine any teaching therein with that of any of the other references to provide Applicants' claimed invention.

For at least the foregoing reasons, none of the cited primary or secondary references could have been combined to provide Applicants' claimed invention. Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Robbins, Sherry, Castellino, Morii, Wiman, Silver, Yago, and Diedrichsen In view of Trese and Hiemstra

The Examiner rejected claims 1-24 as allegedly unpatentable over Robbins, Sherry, Castellino, Morii, Wiman, Silver, Yago, and Diedrichsen, in view of US Pat. No. 6,207,066 to Trese, et al. (Trese) and international published patent application WO 98/37086. Based on the foregoing and following remarks, Applicants respectfully traverse the rejection.

As noted above Robbins, Sherry, Castellino, Morii, and Wiman fail to teach or suggest any step involving an "active plasmin-specific absorbent material." Yago and Diedrichsen also fail to teach or suggest such a step or material. As discussed above, no teaching of Silver could be properly combined with any cited reference to provide Applicants' claimed invention (no motivation). Accordingly, no combination of any teaching thereof could have provided Applicants' claimed invention.

For at least the reason that none of the cited primary or secondary references teach or suggest any step involving an "active plasmin-specific absorbent material," no combination of

any teaching thereof could have provided Applicants' claimed invention. Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Robbins in view of Silver, Trese, Hiemstra, and Diedrichsen

The Examiner rejected claims 1-3, 5-15, and 18-24 as allegedly unpatentable over Robbins in view of Silver, Trese, Hiemstra, and Diedrichsen. Based on the foregoing and following remarks, Applicants respectfully traverse the rejection.

As noted above Robbins, Trese, Hiemstra, and Diedrichsen all fail to teach or suggest any step involving an "active plasmin-specific absorbent material." As discussed above, no teaching of Silver could be properly combined with any cited reference to provide Applicants' claimed invention (no motivation). Accordingly, no combination of any teaching thereof could have provided Applicants' claimed invention.

For at least the reason that none of the cited primary or secondary references teach or suggest any step involving an "active plasmin-specific absorbent material," no combination of any teaching thereof could have provided Applicants' claimed invention. Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Alleged Obviousness-type Double Patenting

Regarding the Examiner's provisional rejection of claims 1-5, 8, 14-16, and 18-24 as allegedly unpatentable over claims 1-8, 10, 11, and 13-20 of co-pending, co-owned Application No. 10/143,156, Applicants request that the rejection be held in abeyance until otherwise allowable subject matter is found. At such time, Applicants will file an appropriate Terminal Disclaimer if a proper basis for the currently provisional rejection exists at that time.

CONCLUSION

Applicants believe that all rejections except the rejection alleged under the judicially-created doctrine of obviousness-type double patenting have been properly traversed or rendered moot. Regarding the provisional obviousness-type double patenting rejection, Applicants have requested that the rejection be held in abeyance until allowable subject matter is found.

It is believed that, pending resolution of the rejection based on obviousness-type alleged double patenting, all claims are in condition for immediate allowance. The Examiner is invited to contact the undersigned at (336) 721-3681 with any questions she may have concerning this submission.

Respectfully submitted,

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